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Evaluation of carotid intima-media thickness of female fibromyalgia patients and determination of their relationship with disease activity, severity of fibromyalgia, anxiety and depression levels

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ABSTRACT

Aim: Carotid artery intima-media thickness is thought strong predictor of cardiovascular diseases. To evaluate the common carotid artery intima-media thickness (CCIMT) in female patients with fibromiyalgia (FM) and determine its relationship with disease activity, severity of fibromyalgia, anxiety and depression levels.

Material and Method: Thirty nine patients who had fibromyalgia syndrome according to 2016 American College of Rheumatology (ACR) classification criteria and 41 healthy controls were included. Pain level and disease activities were assessed with Numerical Rating Scale (NRS) and Fibromyalgia Impact Questionnairre (FIQ) respectively. According to ACR 2016 classification criteria, Widespread Pain Index (WPI), Symptom Severity Score and Hospital Anxiety and Depression Scale (HADS) were performed. The LDL , HDL and Triglyceride levels were evaluated. Bilateral common carotid artery intima-media thicknesses (CCIMT) were performed by a blind radiologist to the groups of participants.

Results: Age, weight and height were similar between groups ($p>0.05$). Triglyceride level was significant higher in patients with FM ($p=0.001$). HDL and LDL levels were similar between groups ($p=0.297$, $p=0.061$). Bilateral CCIMT was significantly higher in patients with FM ($p<0.001$). Bilateral CCIMT were found positively correlated with age in FM group ($r=0.390$, $p=0.014$, $r=0.404$, $p=0.011$ respectively). There were found no correlations between bilateral CCIMT, height, weight, triglyseride level, LDL level, FIQ, NRS, WPI, Symptom Severity Score, HADS scores. .

Conclusion: In FM patients, bilateral CCIMTs were found increased compared to healthy controls. No associations were found between CCIMT, LDL, triglyceride levels, disease activity and pain level, anxiety and depression level in patients with FM.

Keywords: Fibromiyalgia, common carotid artery intima-media thickness, disease activity, anxiety, depression

INTRODUCTION

Fibromyalgia syndrome (FM) is a chronic, painful musculoskeletal disorder of unknown etiology. Fatigue, depression, cognitive dysfunction and headache were shown as symptoms in patients with FM (1,2). Various studies show that oxidative stress may play a role in the pathogenesis of FM (3,4). Increased oxidative stress, which is characterized by protein and lipid oxidation in the vascular wall, plays a role in the development of atherosclerosis (5).

Paraoxonase-1 enzyme is a high-density-lypoprotein (HDL) related antioxidant enzyme which is synthesized in the liver (6). It is thought that decreased paraoxonase activity plays a role in the development of coronary artery disease (7). Oxidative stress causes an increase in carotid intima-media thickness as well as coronary artery disease by making endothelial remodelling (8,9). There are some studies showing that patients with FM are exposed to oxidative stress and their paraoxonase and arylesterase activities are reduced (5). Therefore, it is thought that patients with FM are prone to the development of atherosclerosis(5). Also in FM patients sympathetic activity was thought increased because of pain and stress (10-12). It may cause endothelial damage and cardiovascular diseases (13).

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In literature, carotid intima-media thickness measurement was thought strong predictor of cardiovascular diseases (14). Although there are few studies evaluating bilateral carotid intima media thicknesses in patients with FM, there is no study evaluating the relationship between carotid-intima media thicknesses and disease activity, severity of FM, anxiety and depression in patients with FM. We aimed to evaluate the common carotid artery intima-media thickness (CCIMT) in female patients with FM by using ultrasonography and to determine its relationship with disease activity, severity of FM , anxiety and depression levels.

MATERIAL AND METHOD

This study was carried out with the permission of Hitit University Clinical Researches Ethics Committee (Date: 08.09.2020, Decision No: 330). A well written informed consent was obtained from all participants according to the principles of the Helsinki Declaration.

Thirty-nine patients were admitted to our clinic with a diagnosis of fibromyalgia according to the 2016 ACR classification criteria for fibromyalgia syndrome and 41 healthy controls were included in the study (Group 1: patients with FM, Group 2: healthy controls). Participants with concomitant rheumatic disease, neurological disease; history of other systemic diseases such as hypothyroidism/hyperthyroidism, diabetes mellitus; previous history of overt trauma, history of coronary artery disease, and other cardiac diseases and hypertension or related family history were excluded.

Number of participants was determined assuming a 0.66 mm mean difference and 0.24 mm SD of thickness at common carotid artery intima-media (CCIMT) with 80% power and 5% significance and 35±4 participants were planned to invite the study for each group (15).

Demographic and clinical characteristics were recorded. Pain level and disease activities were assessed with the Numerical Rating Scale (NRS) and Fibromyalgia Impact Questionnaire (FIQ) respectively. The LDL , HDL and Triglyceride levels of participants were evaluated. Venous blood samples were obtained at least after a 12 hour overnight fast and all samples were collected between 07:30 and 09:30 AM. Bilateral CCIMTs were performed by a blind radiologist to the groups of participants.

Fibromyalgia Impact Questionnaire (FIQ): The validity and reliability of the Fibromyalgia Impact Questionnaire (FIQ) for Turkey was assessed by Sarmer et al. (16,17). This scale is composed of 10 items. Physical functioning, well-being, missed work days, difficulty in work, pain, fatigue, morning tiredness, stiffness, anxiety, and depression are measured in this scale. Evaluation was realized over a total of 100 points, including 10 points for each subheading. Low score indicates low severity of disease and high score indicates high severity of disease(16).

Numerical Rating Scale (NRS): is a subjective measurement and pain levels of participants were evaluated on an 11-point numerical scale. It is composed of 0 (no pain) to 10 (worst pain)(18).

Hospital Anxiety and Depression Scale (HADS): It is used to determine anxiety and depression levels (19). It consists of 14 questions and anxiety and depression levels are evaluated with seven questions each. Higher scores indicate increased severity of anxiety or depression. The reliability and validity of the Turkish language version were examined (20). Cut-off scores for Turkish society have been determined as 7 for anxiety and 10 for depression (20).

The measurement of common carotis artery intima-media thickness (CCIMT): While the participant was sitting in the supine position, the measurement was taken by rotating the neck to the left for the right common carotid artery and by rotating the neck to the right for the left common carotid artery. For common carotid artery orientation, first transversal imaging was made from the base of the neck to the carotid bifurcation. The vessel wall was viewed longitudinally, approximately 1 cm below the bifurcation. At least 3 carotid intima-media thickness measurements were made and the averages were determined. If plaque was seen, the presence of plaque was noted. With the optimal B mode setting, gain, dept and focal zones were adjusted to obtain the best image for carotid intima-media thickness and measure (21).

Statistical Analyses

All data were analyzed using the Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, USA) 15.0 program for Windows. Visual and analytical methods were used for the variables for determining whether or not they are normally distributed. Continuous variables were expressed as mean ± SD and nonparametric variables were expressed as median (quartiles). Independent sample t test was used to compared FIQ score, Triglyseride level, HDL level, LDL level, Symptom Severity Score, weight, BMI and left CCIMT. Man Whiney U test was used to compared age, height, NRS, Widespread Pain Index, HADS anxiety and depression scores and right CCIMT. Pearson and Spearman correlation coefficients were used to evaluate the linear relationship between predictive variables. A value of $p < 0.05$ was considered statistically significant.

RESULTS

Thirty-nine patients with a diagnosis of fibromyalgia according to 2016 ACR classification criteria for fibromyalgia syndrome and forty healthy participants were included. All participants were female. There were 16 (41%) patients who used duloxetine and 17 (43.5%) patients who used pregabalin in FM group. Age, height, weight and BMI were similar between groups (**Table 1**) Triglyceride level was significant higher in patients with FM compared to healthy controls (p=0.001). HDL and LDL levels were similar between groups (p=0.297, p=0.061). FIQ score was 67.10±11.56, NRS score was 8 (6-8) in patients with fibromyalgia. Bilateral common carotid artery intima-media thicknesses were significantly higher in patients with fibromyalgia compared to healthy controls (p<0.001). In fibromiyalgia group, there were 1 patient with left common carotid artery plaque and 2 patients with right common carotid artery plaque (p=0.481, p=0.741, respectively). There were no participants with common carotid artery plaque in healthy controls. In FM group, there was no significant difference in right and left CCIMT between patients who used duloxetine and pregabalin (p=0.845 and p=0.822 respectively).

Table 1. Demographic and clinical features of patients with fibromyalgia and healthy controls

	Patients with fibromyalgia n=39	Healthy controls n= 41	p value
Age (year)	44 (37-49)	40 (30-45)	0.051
Height (cm)	164 (160-167)	165 (158.5-168)	0.873
Weight (kg)	71.08 ± 8.6	67.24± 12.6	0.115
BMI (kg/m²)	26.85± 3.74	25.27± 4.74	0.104
Disease duration (month)	36 (12-60)		
FIQ (score)	67.10±11.56		
NRS (score)	8 (6-8)		
Widespread pain index (WPI)	8 (6-11)		
Symptom severity score	8.1± 1.79		
Triglyceride (mg/dL)	193.05±148.55	99.9±46.9	0.001
HDL (mg/dL)	54.66±12.01	52.12±8.94	0.297
LDL (mg/dL)	128.68±46.33	110.131±31.82	0.061
HADS anxiety score	6 (4-10)	2 (2-3)	<0.001
HADS depression score	6 (4-9)	2 (2-3)	<0.001
Right carotid intima-media thickness (mm)	0.69 (0.65-0.73)	0.48 (0.44-0.56)	<0.001
Left carotid intima-media thickness (mm)	0.69±0.11	0.51±0.12	<0.001

HADS: Hospital Anxiety Depression Scale. Data are presented as mean±standard deviation or median and quartiles. p<0.05

Bilateral CCIMT were found positively correlated with age (**Table 2**). HDL level was found negatively correlated with left CCIMT (**Table 2**). There were found no correlations between bilateral CCIMT, height, weight, BMI, triglyseride level, LDL level, FIQ, NRS, Widespread Pain Index (WPI), Symptom Severity Score, HADS anxiety and depression scores (**Table 2**).

Table 2. Correlation between carotid intima-media thicknesses and clinical features in fibromyalgia patients

	Right carotid intima-media thickness		Left carotid intima-media thickness	
	r	p	r	p
Age	0.390	0.014**	0.404	0.011**
Height	-0.029	0.863**	0.025	0.881**
Weight	0.198	0.227**	0.207	0.207**
BMI	0.208	0.204**	0.215	0.188*
Disease duration	0.008	0.961**	0.137	0.404**
FIQ score	-0.086	0.603**	-0.023	0.889*
NRS score	-0.260	0.110**	-0.239	0.142**
Triglyceride level	0.086	0.607**	0.038	0.823*
HDL level	-0.312	0.057**	-0.393	0.015*
LDL level	0.135	0.462**	0.235	0.196*
Widespread pain index (WPI)	0.067	0.684**	0.055	0.740**
Symptom severity score	0.036	0.827**	-0.043	0.795*
HADS anxiety score	-0.146	0.375**	-0.184	0.262**
HADS depression score	-0.165	0.317**	-0.199	0.224**

*: Pearson correlation, **: Spearman correlation

DISCUSSION

Our results demonstrated that common carotid artery intima-media thicknesses were increased bilaterally in patients with fibromyalgia. We found that there was an association between age and bilateral common carotid artery intima-media thicknesses. Also there was an association between blood HDL level and left common carotid intima- media thickness. In the literature there are a few studies evaluating common carotid intima-media thicknesses in patients with FM. One study was done Bölük et al. (22) and they found that carotid intima-media thicknesses were increased in patients with FM. But they did not describe how they measured carotid intima-media thicknesses or which carotid artery intima-media thicknesses (internal carotid artery, external carotid artery or common carotid artery) were measured. Low number of patients participated to their study. We evaluated the drug usage and disease duration and found that CCIMTs were similar in both FM patients who used duloxetine and pregabalin in our study. But they did not evaluated the relationship between disease duration or using drug and carotid intima-media thicknesses. Also differently from our study, they did not evaluate the association between carotid intima-media thicknesses and anxiety and depression levels. In a study which evaluated the relationship between endocan levels and carotid intima-media thickness in patients with FM, serum endocan levels and carotid intima-media thickness were found

significantly higher in patients with FM (23). This study supports to our results but we did not evaluate serum endocan level or other inflammatory marker with blood labratory test in our study. Although these two studies examined carotid intima-media thickness in patients with FM, there is no study in the literature designed as comprehensive as our study.

In FM patients, stress and pain were known related with increased activity of sympathetic nervous system (10-12). Sympathetic hyperactivity may contribute to endothelial damage and cause cardiovascular diseases (13). So increased chronic pain may cause endothelial dysfuction and increased common carotid artery intima-media thickness. In the U.S. National Health Interview Survey, myocardial infarction was found more common in patients with FM than in patients without FM (24). Also, in a Taiwanian study, the risk of coronary heart disease was found increased in patients with FM (25). The results of our study support to the increased risk of cardiovascular diseases. In many studies, carotid intima-media thickness measurement was found successful for assessment of cardiovascular disease risk (26-30). Carotid intima-media thickness measurement was shown independently predictive measurement for old and young subjects in future vascular events (14). Also, brain infarction was found associated with increased common carotid artery intima-media thickness (29). However most participants were middle-aged in our study and we found that bilateral CCIMTs were higher in patients with FM. But we did not find any association between bilateral CCIMT, disease activity, severity of FM, pain, anxiety and depression levels. According to our study, it can be concluded that increased disease activity, anxiety or depression levels do not increase CCIMT in patients with fibromyalgia. Our results support the predisposition to atherosclerosis diseases in patients with FM. Therefore, stroke and cardiovascular diseases are expected to be more common in patients with FM. So we could predict cardiovascular disease performing ultrasonography for measuring CCIMT.

Tseng CH et al. (31) found that diabetes mellitus, hypertension, hyperlipidemia and coronary artery disease were more prevalent in fibromyalgia patients than healthy controls. Also they showed an increased risk of cumulative stroke in patients with fibromyalgia in a 3-year follow up cohort study. Age is an important risk factor for stroke (31). We found that there was an association between age and bilateral common carotid artery intima-media thicknesses. In their study, the stroke weight was found relatively higher in the younger population in patients with FM. Because stroke-related comorbidities were found more common in the patients with FM (31). Similar to this study, we found that triglyceride level was higher in patients with FM. But we found that HDL and LDL level were similar in patients with FM and healthy controls. In this and our study most participants were middle-aged. We did not evaluate the presence of hypertension and diabetes mellitus in patients with FM in our study. Because we excluded the participants with hypertension and diabetes mellitus from our study. The lack of difference in LDL levels between patients and healthy controls in our study may be due to the exclusion of patients with diabetes mellitus and hypertension from our study.

Headache and impaired sleep quality are common known symptoms in patients with FM. Tatar IG et al. (32) said that carotid intima-media thickness was increased in patients with migraine. Brutto OH et al. (33) showed that there was an association between sleep quality and increased carotid intima media thickness. So one of the causes of headache and impaired sleep quality in patients with FM may be the increased CCIMT. But we did not evalute the sleep quality in our study.

To the best our knowledge, this is the first study evaluating the relationship between common carotid artery intima media thicknesses and disease activity, disease duration, severity of FM, pain, anxiety and depression levels in patients with FM. Inclusion of sufficients number of patients, making the ultrasonographic measurements by a blinded radiologist, addition to disease activity evaluation of pain level, severity of FM, anxiety and depression levels are the superior aspects of our study. We think that this study will provide valuable contributions to the literature and clinical practice in terms of early recognition and prevention of cardiovascular diseases in patients with FM. But there are some limitations in our study. Exclusion of male patients with FM and measurement of only common carotid artery intima-media thicknesses, single-site location of the investigation may be some limitations of our study.

CONCLUSION

This study shows that in fibromiyalgia patients, bilateral carotid artery intima media thicknesses were found increased compared to healthy controls. If increased carotid artery intima-media thickness was thought a strong predictor of cardiovascular events, patients with fibromylagia should be followed up more carefully in terms of cardiovascular events in long term. No association were found between carotid intima-media thickness, LDL, triglyceride levels, disease activity, severity of fibromyalgia, anxiety, depression and pain level in patients with fibromiyalgia.

ETHICAL DECLARATIONS

Ethics Committee Approval: This study was carried out with the permission of Hitit University Clinical Researches Ethics Committee (Date: 08.09.2020, Decision No: 330).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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